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Comparison between Children Treated at Home and Those Requiring Hospital Admission for Rotavirus and Other Enteric Pathogens Associated with Acute Diarrhea in Melbourne, Australia

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The etiology of acute diarrhea in children less than 42 months of age attending one pediatric hospital in Melbourne, Australia, was studied during a 7-month period encompassing the winter of 1984. Pathogens identified in 157 children treated as outpatients with mild disease were compared with those in 232 children hospitalized with severe disease. The pathogens (and frequencies among outpatients and inpatients, respectively) detected were rotaviruses (32.5 and 50.9%), enteric adenoviruses (8.9 and 7.4%), *Campylobacter jejuni* (7.2 and 1.3%), and *Salmonella* sp. (4.0 and 1.7%). Electropherotypes of rotavirus strains from outpatients and inpatients were compared. Two strains predominated during the 7 months of this study and were observed with equal frequency from outpatients and inpatients. Rotaviruses of the same electropherotype caused a wide spectrum of disease, with symptoms ranging from mild to severe, life-threatening diarrhea. The similarity of etiological agents identified from children with mild and severe forms of acute diarrhea suggests that the etiology of community enteric illness can be reasonably inferred from the etiology of inpatient disease in children in the same geographic area. During the winter epidemic period, the severity of symptoms associated with rotavirus infection in young children is likely to be determined by the inherent susceptibility of the host rather than by genetic differences in the strains of infecting rotaviruses.

Acute diarrhea is a common cause of ill health in young children. Symptoms vary widely in severity. Attack rates reported from the United States for children 0 to 4 years old are 120 diarrheal episodes per 100 children per year. Twenty of these episodes are severe enough for parents to seek medical attention, and one of those episodes is severe enough to warrant hospital admission (15–17, 21). A prospective study of 1,210 normal New Zealand children followed from birth showed that 37 of every 100 children under 4 years of age suffered from acute diarrhea requiring medical attention each year and 1 of every 100 children required hospital admission (10).

During the past 10 years, significant advances have been made in elucidating the etiology of severe acute diarrhea in childhood, and a recognized enteric agent can now be identified from the majority of children requiring hospitalization (11). There have been relatively few studies of etiological agents of milder diarrhea in young children not requiring admission to hospitals (2, 4, 7, 15, 17). These studies have often failed to identify etiological agents in a majority of patients, and it has been suggested that the etiological agents of mild diarrhea may differ from those of severe diarrhea (17).

Most studies have not compared etiological agents simultaneously responsible for mild and severe diarrhea in children in the same community. Consequently there is little evidence that children admitted to hospitals with acute diarrhea may be infected with a spectrum of enteric pathogens different from that of children whose diarrhea can be satisfactorily treated at home. It is important to understand the etiology of less severe illness to design successful strategies to control this disease.

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MATERIALS AND METHODS

The Royal Children's Hospital in Melbourne, Australia, is a general pediatric 400-bed hospital drawing the majority of its primary-care patients from families in inner surburban areas. Initially most children with acute diarrhea present at the Emergency Department of the hospital, where a triage nurse assesses their clinical status. Children requiring urgent attention are admitted immediately to the infectious diseases ward. Nonurgent patients are directed to the General Clinic, which is similar to a primary-care facility and is adjacent to the Emergency Department. Patients are seen by a resident medical officer who assesses the severity of the illness and degree of dehydration. Those with moderate or severe dehydration are then admitted to the infectious diseases ward. Those with mild or no dehydration are treated as outpatients during the first visit and admitted to the infectious diseases ward at a subsequent visit if necessary.

Patient selection. Children included in this study all had a primary diagnosis of acute diarrhea, defined as diarrhea of sudden onset (with or without vomiting), of less than 10-day duration, and with no other cause for the symptoms. This definition is consistent with those used in similar studies (13, 22). All children presented at the Royal Children's Hospital during April through October 1984 and were less than 42 months old.

Group A. The 157 children making up group A had acute diarrhea that was treated at home after their initial attendance at the General Clinic. The general clinic was visited every 1 to 2 days by one of the investigators (G.P.) to recruit patients, and a child was selected for the study if he or she had acute diarrhea as defined, was judged by a resident medical officer as not sufficiently ill to require hospitalization, and had provided a stool specimen within 24 h of

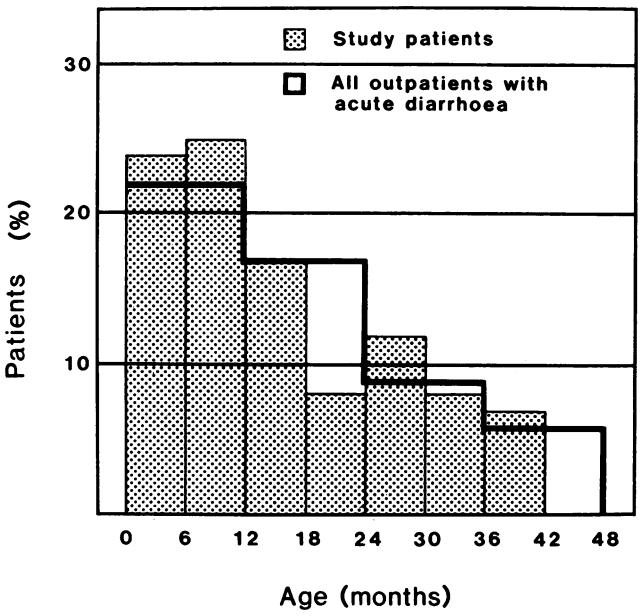

FIG. 1. Age distribution of outpatient population studied compared with that of all outpatients with acute diarrhea.

presentation. Stool samples were obtained in the General Clinic whenever possible. If no specimen was available, the parents were provided with containers and requested to return with a specimen from the patient within 24 h. Children admitted to the hospital at a subsequent visit were later excluded from the study.

A total of 157 children (84 male) was enrolled, representing 30% of the possible study population. Monthly totals for recruits were 25 (April), 25 (May), 23 (June), 32 (July), 22 (August), 17 (September), and 13 (October). The majority (70%) of patients were less than 24 months of age, and 50% were less than 12 months. The age distribution of study patients for each 6-month age group was similar to the age distribution of all children presenting to the General Clinic with acute diarrhea during the same period (Fig. 1). The average duration of symptoms at the time of enrollment was 4 days (range 1 to 10). Only 7% (11/157) of the children had been ill for longer than 1 week.

Group B. Group B comprised children admitted on their initial visit to the hospital for treatment of acute diarrhea associated with moderate or severe dehydration or with persistent vomiting. Stool specimens from 232 children (130 male) representing 85% of the possible study population were obtained within 24 h of admission. Monthly patient totals were 41 (April), 53 (May), 36 (June), 39 (July), 36 (August), 20 (September), and 17 (October). The majority (71%) of the children were less than 24 months old, and 37% were less than 12 months old. The average duration of symptoms in the children admitted to the hospital was 3 days (range 1 to 10). Only 3% of the children had been ill for longer than 1 week.

Processing of samples. Samples were divided into aliquots, depending on the quantity of available stool, and were stored at 4°C for up to 12 h before cell culture or for 1 to 2 weeks before examination by electron microscopy (EM) or enzyme immunoassay (EIA). All 157 specimens from group A were examined for rotavirus by EIA and EM. In addition, 125 were examined for bacterial pathogens, and 112 were also examined for adenovirus by EIA and cell culture. For group B, 230 of 232 patients were examined for bacterial pathogens. Furthermore, 220 were examined for viruses by EM or EIA or both, and 189 were also examined by cell culture.

Bacteriology. Fecal specimens were examined for *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., enteropathogenic *Escherichia coli*, and *Yersinia enterocolitica*. Specimens were cultured with media manufactured from materials (Oxoid Ltd.) subjected to quality control on the site. Fecal specimens were plated onto Columbia agar plus 5% horse blood–Desoxycholate-Citrate Agar–xylose lysine Desoxycholate agar–Sabouraud agar–*Yersinia* selective agar and incubated in air at 37°C for 18 to 24 h. *Campylobacter* selective agar was inoculated and incubated in 10% CO_2 for 48 h at 42°C. Specimens were replated on xylose lysine Desoxycholate agar after enrichment in Selenite broth at 37°C. The *Campylobacter* sp. isolated was confirmed by sensitivity patterns and catalase and oxidase reactions. The examination for intestinal parasites was performed by phase-contrast microscopy. An ether-Formalin concentration was applied to suitable specimens.

Virology. EM was used to detect viruses shed in feces (rotaviruses, adenoviruses, and small viruses). The method incorporated the concentration of a clarified fecal homogenate (10%) with polyacrylamide hydrogel before negative staining (24). Samples were also tested by rotavirus EIA with guinea pig and rabbit antisera raised against simian rotavirus SA-11 (19). All rotavirus-positive fecal samples were examined by polyacrylamide gel electrophoresis by the method of Herring et al. (12) as modified by Dyall-Smith and Holmes (8). Rotaviruses giving a visible gel pattern were allotted to electropherotypes arbitrarily designated A to I. All strains with apparently similar patterns were subjected to coelectrophoresis to confirm their identity. EIA for adenoviruses was performed on the fecal supernatants with antibody to adenovirus hexon antigen raised in guinea pigs and rabbits (23).

Cultivable viruses were identified after inoculation onto human diploid fibroblast, primary cynomolgus monkey kidney, and HeLa cell monolayer cultures. Feces were inoculated into cell cultures after a 10% (wt/vol) dilution in phosphate-buffered saline (pH 7.2) and centrifugation at 600 × *g* for 5 min. Primary isolates were subpassaged into fresh cultures and typed by serum neutralization with appropriate specific antisera.

Statistical analysis was performed by the chi-square test with Yate's correction when applicable.

RESULTS

Enteropathogens identified in feces from outpatients and inpatients are presented in Table 1. Since the total numbers

TABLE 1. Etiology of acute diarrhea in children treated as outpatients or inpatients from April to October 1984

Etiological agent	% with disease among group:	
	A (outpatient)	B (inpatient)
Rotavirus	32.5	50.9
Adenovirus (enteric)	8.9	7.4
Enterovirus	1.8	2.6
Campylobacter jejuni	7.2	1.3
Salmonella sp.	4.0	1.7
Shigella sp.	0	1.7
E. coli (enteropathogenic)	0.8	0.9
Mixed infections	1.8	3.9

of specimens examined differed for each pathogen, the results have been presented as percentages. The same range of enteric pathogens in the same order of importance was identified in outpatients (group A) and in inpatients (group B). Overall, at least one enteric pathogen was identified in 55.2% of the outpatients and in 66.5% of the inpatients.

Rotaviruses were detected by EM or EIA or both in 51 of 157 (32.5%) specimens obtained from outpatients and in 118 of 232 (50.9%) specimens from inpatients. Adenoviruses were identified in 14 of 112 outpatients by EM or EIA or both. Of the 14 adenoviruses from outpatients, 4 grew in cell cultures and were identified as adenovirus type 2 (3 cultures) or type 1 (1 culture). The remaining 10 adenoviruses either failed to grow (6 cultures) or produced initial cytopathic effects but could not be passaged further.These 10 were regarded as enteric adenoviruses. Adenoviruses were also identified in 19 of 189 inpatients; 15 of these viruses were regarded as enteric adenoviruses. In addition, adenovirus types 1 (two) and type 2 (three) were isolated. Enteroviruses were cultured from 10 of the 112 specimens examined from outpatients. Eight of these enteroviruses were identified as oral polio vaccine virus. The remaining two could not be typed. Enteroviruses were cultured from 7 of 232 inpatients. Two cultures were positive for oral polio vaccine virus.

Bacterial pathogens were identified in 12.0% of the outpatients and 3.9% of the inpatients. *C. jejuni*, *Salmonella* spp., and *E. coli* serotype $O_{111}K_{58}B_4$ were identified in nine, five, and one outpatient child, respectively, and in three, four, and two children admitted to the hospital. There was a statistically significant difference between isolation rates of *C. jejuni* in outpatients and inpatients ($P < 0.01$). Mixed infections were detected in 2 of the 112 outpatients on whom all diagnostic tests were performed. These mixtures comprised rotavirus and *Salmonella* spp. (one) and rotavirus and *C. jejuni* (one). Mixed infections detected in 7 of 180 children admitted to the hospital comprised rotavirus and *Salmonella* spp. (two), rotavirus and *C. jejuni* (two), rotavirus and adenovirus (one), rotavirus and *E. coli* $O_{111}K_{58}B_4$ (one), and enteric adenovirus and *Salmonella* sp. (one).

The occurrence of enteric pathogens was analyzed in relation to age. Rotaviruses were identified more often in both outpatients and inpatients 6 months or more old (Table 2) than in the younger age group. The difference was statistically significant in children admitted to the hospital ($P < 0.001$). Rotaviruses were identified significantly more often in inpatients than in outpatients among children 6 months or more old ($P < 0.01$). *C. jejuni* was isolated significantly more often ($P < 0.01$) from children treated as outpatients who were aged 24 to 41 months (6/36) than from younger children (3/89). No significant difference in the occurrence of other enteric pathogens in relation to the ages of inpatients or outpatients was detected. No pathogens were identified in 57% of the outpatients 0 to 5 months old, 43% of those 6 to 23 months old, and 37% of those 24 to 41 months old. No enteric pathogen was identified from 57% of those 0 to 5 months old, 26% of those 6 to 23 months old, and 20% of those 24 to 41 months old among the inpatients.

TABLE 2. Occurrence of rotaviruses in patients with acute diarrhea in relation to age and place of treatment

Age (mo)	No. rotavirus positive/no. tested (%)	
	Outpatients (n = 157)	Inpatients (n = 220)
0-5	9/38 (23.7)	8/44 (18.2)*[a]
6-23	26/77 (33.8)†	74/127 (58.3)*†
24-41	16/42 (38)‡	33/49 (67.3)‡

[a] P values were calculated for the pairs with the following symbols by the chi-square test (with Yate's correction when applicable): *, $P < 0.001$; †, $P < 0.01$; ‡ $P < 0.01$.

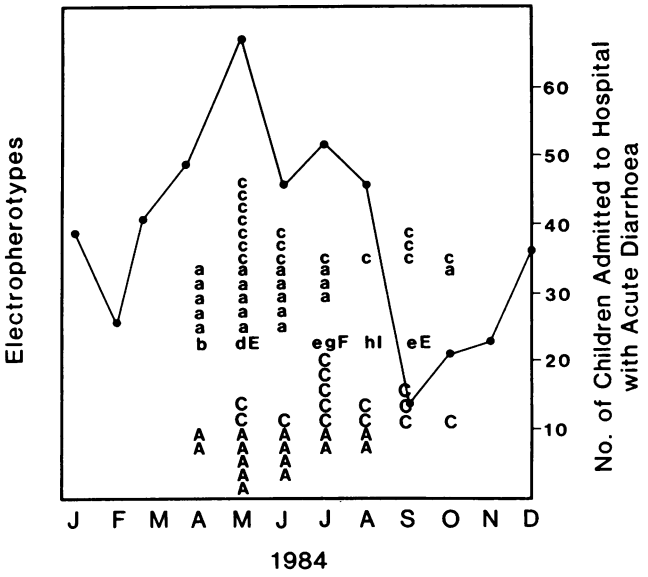

FIG. 2. Occurrence of rotavirus electropherotypes in individual outpatients (A to I) and inpatients (a to h) in relation to monthly hospital admissions for acute diarrhea during April through October 1984.

Rotavirus electropherotypes. A characteristic rotavirus genome pattern was obtained by gel electrophoresis of fecal extracts from 33 of 51 rotavirus-positive specimens tested from outpatients and from 41 of 118 positive specimens tested from inpatients. Nine different electropherotypes (arbitrarily designated A to I in chronological order of detection) were found in the 74 samples. All were long-pattern strains. During the 7 months of the study, electropherotypes A and C were predominant, comprising 86% of all the strains identified (Fig. 2). Only one other rotavirus electropherotype, E, was observed more than once. These three electropherotypes were observed with approximately the same frequency in inpatients and outpatients. The monthly occurrence of each electropherotype is illustrated in Fig. 2. Each letter denotes identification of that particular electropherotype from a single patient. For each electropherotype outpatients are identified by capital letters and inpatients are indicated by lowercase letters. The age range of children infected was similar for both predominant electropherotypes in inpatients and outpatients. Outpatients infected with electropherotype A had a mean age of 15.5 months (range, 2 to 33 months). Those infected with electropherotype C had a mean age of 13.5 months (3 to 40 months). The corresponding results for inpatients infected with electropherotype a or c were 16.1 months (5 to 39 months) and 16.4 months (4 to 42 months). Electropherotypes b, d, g, and h were found only in inpatients, and electropherotypes F and I were found only in outpatients.

Gels resulting from the coelectrophoresis of A and C are shown in Fig. 3. Differing rates of migration were observed for genes 2 through 10. The serotype of these strains has since been identified with serotype-specific monoclonal antibodies raised in our laboratories. Electropherotype A is a

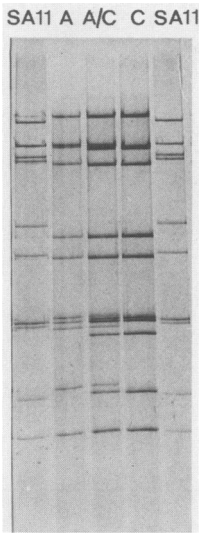

FIG. 3. Gel electrophoresis patterns of genome RNA extracted from rotavirus strains. SA11, simian rotavirus strain; A and C, human rotavirus strains; A/C, coelectrophoresis of A and C. Migration was from top to bottom.

serotype 1 strain, and electropherotype C is a serotype 4 strain.

Electropherotype A was present in both outpatients and inpatients at the start of the study period (Fig. 2). It was equally common in both groups from April to July and uncommon in both groups after July. The new electropherotype C appeared simultaneously in outpatients and inpatients during May, coincident with the peak month for hospital admissions. This peak month was characterized by the coexistence of the two strains A and C. Electropherotype C was initially more common in inpatients than in outpatients but became more common in outpatients after 3 months. It was the predominant strain identified after the winter peak for hospital admissions. Electropherotype E was detected in May, July, and September. The electropherotypes that were detected once only (B, D, F, G, H, and I) occurred sporadically throughout the seven months.

DISCUSSION

This comparison of enteric pathogens isolated from young children with diarrhea of differing severity showed a similar range of pathogens in inpatients and outpatients. Identification of an etiological agent was more common in inpatients, where an enteric pathogen was found in 65% of the children, compared with 53% of the outpatients. This difference was not likely to have been due to an artefact of patient selection, because the two groups were well matched for age and sex and most children in both groups came from homes located in the same inner-suburban areas. The increased recovery rate of enteric pathogens in inpatients may have been partly due to their earlier presentation to a treatment facility, as the average duration (3 days) of symptoms was less than in the outpatient group (4 days). It is possible that the amount of a pathogen excreted by children with a mild disease was less than the minimum amount detectable by current diagnostic techniques.

The cause of acute diarrhea was particularly difficult to determine in children less than 6 months old, among whom an enteric pathogen was identified in only 43% of those tested. This age group requires more intensive study, perhaps by serological techniques that are more sensitive than what was used for the diagnosis of infection with known pathogens and by techniques designed to reveal new pathogens.

Enteric pathogens identified in these Melbourne children showed a similar order of importance in inpatients and outpatients. Variations in the monthly incidence of pathogens in the two populations followed the same pattern. In both groups, viral infections (predominantly rotavirus) were much more common than were bacterial infections. This result was partly due to bias as a result of the implementation of the survey during the months incorporating the seasonal peak for rotavirus infections (April to October 1984) and the exclusion of the seasonal peak (February and March) for bacterial infections (6).

Rotaviruses were more common in inpatients than in outpatients, which emphasizes the severity of symptoms associated with this agent. Enteric adenoviruses were identified frequently in inpatients (7.4%) and outpatients (8.9%). For the purposes of this study, enteric adenoviruses were defined as adenoviruses that were identified from feces by EM or adenovirus group-specific EIA and that failed to grow and be passaged in standard cell cultures. This definition excluded patients who excreted the more common types of cultivable adenoviruses. It is probable that the enteric adenoviruses identified in our study belonged to adenovirus types 40 and 41. These serotypes have recently been shown to be implicated in the etiology of acute diarrhea in 5 to 10% of the children hospitalized for treatment in the United States or Sweden (5, 22). In our study, enteric adenoviruses were slightly more common in infants less than 6 months old than in older children. Untyped enteroviruses and small viruses were found in 2 to 3% of the patients. This low rate of detection is consistent with other studies (5, 12), and their significance remains uncertain.

C. jejuni and *Salmonella* spp. were the most common bacterial pathogens isolated. Both were isolated more often in outpatients than in inpatients. *C. jejuni* was found significantly more often in outpatients 24 or more months old than in younger children. Enteropathogenic *E. coli* and *Shigella* spp. were found in only 1 to 2% of the samples, and *Y. enterocolitica* was not detected. These results are similar to those reported in other Australian studies in eastern states (1, 6, 13, 18), and all appear to be infrequent in this country.

The detailed analysis of rotavirus electropherotypes identified during this study showed that children who required admission to the hospital were not infected with a different (possibly more virulent) strain of rotavirus than children who could be treated at home. Identical strains of each electropherotype were present in inpatients and in outpatients of similar ages during each month. It seems likely that strains of rotavirus identified in hospital-based studies are representative of strains distributed in the community and that individual strains cause a wide spectrum of clinical symptoms. Variations in the severity of disease in individual children are probably due to variations in host susceptibility rather than to variations in the virulence of infecting strains.

There was a change in the prevalent electropherotype during the winter study period. In April 1984 a strain previously identified from children hospitalized during the winter of 1983 was dominant. The winter peak for diarrhea was marked by the appearance of a second major electropherotype in inpatients and outpatients simultaneously. This new strain was subsequently shown to be a different serotype. The sequential appearance of rotavirus electrophe-

rotypes has been noted by other workers (9, 14, 20), but the widespread distribution of identical electropherotypes in nonhospitalized children with diarrhea has not previously been described.

In a longitudinal serological study of children for the first 3 years after birth, asymptomatic rotavirus infections were frequently identified during winter months (3). It is possible that the strain identified in young children each winter may also be the cause of asymptomatic infections widely spread throughout the community. If so, then it should be possible to predict community exposure to different rotavirus serotypes by examination of the annual patterns of infection derived from hospital-based studies.

The results of this study suggest that in young children with diarrhea severe enough to cause parents to present the child for medical treatment, the etiological agents are similar whether or not the treatment requires admission to the hospital. This means that the etiology of mild gastroenteritis may reasonably be inferred from knowledge of etiological agents identified from hospital patients. If this observation holds true elsewhere, then it may permit understanding of the etiology of mild enteric illness in areas of the world where diagnostic facilities are limited to hospital-based studies.

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